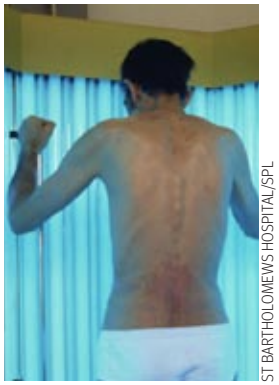
Home UVB phototherapy for psoriasis

Is as safe and effective as outpatient treatment, but provision is poor



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RESEARCH, p 1181

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Psoriasis is a common chronic inflammatory skin condition that causes substantial disability in affected people and their families. In the linked randomised controlled trial, Koek and colleagues assess whether home ultraviolet B (UVB) phototherapy is as safe and effective for psoriasis as conventional UVB phototherapy given in the outpatient department.[1]

UVB has been used to treat psoriasis for more than 75 years, initially in combination with crude coal tar,[2] and later as monotherapy.[3] UVB has been the phototherapy of choice for psoriasis since it was found to be less carcinogenic than PUVA (psoralen plus ultraviolet A phototherapy),[4] and since the development in the late 1980s of a highly efficacious UVB lamp, termed "narrow band UVB."[5]

Patients taking a course of UVB treatment usually attend their local dermatology unit three times each week for eight to 10 weeks. In many cases this leads to complete or almost complete clearance of disease. The duration of clearance is variable but often persists for months. In spite of this impressive efficacy and relatively few side effects, few patients with psoriasis receive UVB treatment. In the NHS most patients with psoriasis are managed in primary care, where phototherapy is seldom available. Dermatology units in the United Kingdom and other developed countries typically cover large geographical areas with a single phototherapy unit in a central "hub and spoke" model. When patients' travelling time, loss of earnings, and travel costs are considered, only those living locally to a phototherapy unit can be expected to attend up to 30 times in a 10 week period.

Home phototherapy for psoriasis was introduced in Sweden in the late 1970s to treat patients living far from their local phototherapy unit.[6] Subsequent open uncontrolled studies in rural United States,[7] the Netherlands,[8] and Scotland[9] confirmed the feasibility of this model and were generally positive about outcomes. Despite this, few dermatologists have embraced home phototherapy; when asked why not, they cite inferior efficacy and higher risks, despite the absence of evidence to support these assumptions.[10] Thus, home phototherapy remains unavailable to most patients with psoriasis.

To date, research on home phototherapy has been limited to open studies assessing its practicalities. No trials have compared home phototherapy with conventional hospital based phototherapy. Koek and colleagues' trial is a pragmatic study that compares home UVB with outpatient UVB as part of normal clinical practice.[1] In addition to assessing the safety and efficacy of the two treatments, they also examined quality of life, burden of treatment, and patient satisfaction. The study found that the treatments had similar efficacy, cumulative doses of UVB, and rates of short term side effects. However, the burden of treatment was significantly lower for patients treated at home, and these patients were more positive about the treatment. Improvements in quality of life were similar for both groups. Basic health economic data from Scotland comparing the two different models of care previously concluded that home phototherapy was cost effective.[9] More detailed health economic analysis is now needed to clarify the cost implications of hospital based UVB phototherapy and home UVB phototherapy.

What are the implications of this study's results for clinical practice? The study highlights an important gap in the provision of treatment for patients with psoriasis. With new potent, but costly, biological treatments now widely available for moderate to severe psoriasis, it is timely to reassess conventional treatments such as UVB. It would be inappropriate for patients to receive these new and expensive treatments when the infrastructure to deliver well established cheaper treatments, such as UVB, is lacking.

Dermatologists should reflect on the shortcomings of current phototherapy services, where many patients are excluded because they live too far from their local unit. The case for home provision of UVB phototherapy for psoriasis is most persuasive in sparsely populated areas. Experience in Germany, the US, the Netherlands, and Scotland confirms that it would be feasible and practical to implement home based UVB phototherapy.[10]

How can home based phototherapy become a reality? Now that safety and efficacy concerns have been tackled, an economic assessment of different UVB service models is needed. This should include the costs of the equipment, costs of teaching patients how to use the equipment, and costs for a clinical governance system within which home phototherapy can operate. Meanwhile, healthcare commissioners should work with local dermatologists to improve access to UVB phototherapy services. A pragmatic interim solution to create more accessible and equitable UVB services might be to deliver phototherapy from "spokes" as well as, or instead of, the "hub."

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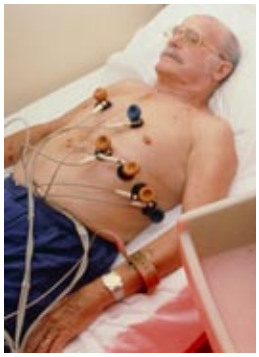
Natriuretic peptides in acute myocardial infarction

Their role in treatment remains uncertain



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Elderly patients form an increasingly large proportion of people with acute myocardial infarction, and advanced age is a strong predictor of a high risk of death or of serious complications after acute myocardial infarction.[1] Paradoxically, elderly patients with acute myocardial infarction have been excluded or under-represented in most clinical trials, and limited data are available to guide their care. Studies of prognosis after acute myocardial infarction in the elderly are also scant,[2] and it is unclear whether or not the established predictors of high risk of death after acute myocardial infarction in the general population are useful in the elderly.

In the linked study, Lorgis and colleagues studied a non-selected cohort of 3291 patients with acute myocardial infarction and showed that circulating concentrations of the N-terminal fragment of B type natriuretic peptide (BNP) prohormone (NT-ProBNP), had an incremental prognostic value in elderly patients, beyond established prognostic markers, such as left ventricular ejection fraction and the GRACE (global registry of acute coronary events) risk score.[3] Indeed, the combination of high GRACE risk scores and increased age adjusted NT-ProBNP concentrations in elderly patients with myocardial infarction revealed a group with a high risk of death (47%) at one year of follow-up.[3] A previous study reported the independent predictive value of NT-ProBNP values in a small sample (n=161) of elderly patients with acute myocardial infarction.[4] Lorgis and colleagues' large study, which extensively adjusted for important covariates, draws further attention to whether NT-ProBNP should be used routinely in elderly patients with myocardial infarction.[3]

BNP belongs to the natriuretic peptide family, a group of structurally similar but genetically distinct peptide hormones that play a major part in cardiovascular, endocrine, and renal homoeostasis. Although the atrial (A type) natriuretic peptide was the first to be described, sequenced, and synthesised,[5] it was BNP—secreted mainly by the ventricular myocardium—that rapidly evolved from physiological research into clinical practice.[6] NT-ProBNP has a longer half life and higher circulating concentrations than BNP. It also fluctuates less and is influenced more by renal function.[7] For most practical indications BNP and NT-ProBNP are interchangeable, and which one is measured will depend on local preferences and availability. However, clinicians must understand their differences and that absolute concentrations are not interchangeable.[7]

The role of BNP and NT-ProBNP measurements has been more comprehensively studied in heart failure, where it has an established role in diagnostic and prognostic evaluation, but it may also be useful for assessing severity, screening in high risk populations, and guiding treatment.[7] In acute coronary syndromes, BNP or NT-ProBNP measurements have been used in risk stratification. Substudies of several large scale clinical trials, as well as observational studies, have consistently associated higher circulating concentrations of BNP and NT-ProBNP with more frequent adverse cardiovascular events and higher mortality in acute coronary syndromes.[8] Although left ventricular systolic or diastolic dysfunction caused by myocardial ischaemia may be the most obvious mechanism of increased BNP or NT-ProBNP values in acute coronary syndromes, there is now robust evidence that hypoxia and ischaemia may directly induce the synthesis and secretion of natriuretic peptides.[8 9]

The data derived from experimental studies are supported by clinical findings. These show that BNP rises after temporary myocardial ischaemia induced by balloon inflation during coronary intervention.[10] NT-ProBNP concentrations are also higher in patients with persistent ST segment elevation after acute myocardial infarction, a non-invasive marker of failure of reperfusion at tissue level.[11] In addition, high NT-ProBNP concentrations are associated with residual myocardial ischaemia in patients with acute myocardial infarction and preserved left ventricular ejection fraction.[12] The importance of hypoxic and ischaemic mechanisms in increasing BNP and NT-ProBNP concentrations in acute coronary syndromes is supported by Lorgis and colleagues' findings—NT-ProBNP was a strong prognostic marker in elderly people with acute myocardial infarction, independently of the GRACE score, troponin concentrations, and left ventricular function.[3]

Could BNP or NT-ProBNP concentrations therefore be used to help identify patients with acute myocardial infarction who will have a poor prognosis, frequent reperfusion failure, and post-acute myocardial infarction ischaemia, in whom more aggressive treatment could reduce cardiac events and improve survival? Unfortunately, the present study does not test this hypothesis. The ability to recognise a high risk subgroup of patients is seldom sufficient to guarantee the routine use of a new test in clinical practice, unless it can change the treatment strategy used. No prospective study has evaluated whether a more aggressive approach should be used in patients with acute myocardial infarction and high BNP or NT-ProBNP values, whether they are elderly or not.

Although the prognostic value of BNP or NT-ProBNP in elderly patients with acute myocardial infarction is indisputable, further research is needed to determine its role in defining therapeutic strategies. Until prospective data become available, BNP or NT-ProBNP measurements should not be performed routinely in elderly people with acute myocardial infarction.

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Treating failed asylum seekers in the NHS

Is humane, but puts pressure on finite resources

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The recent Court of Appeal judgment on the Palestinian asylum seeker identified as YA raises difficult questions about the rights of failed asylum seekers to free NHS care.[1] Asylum claims often involve appalling human tragedy and claimants may need medical treatment. Every doctor's instinct will be to cater for their needs.[2] And there are good public health reasons for doing so to protect the wider community. However, the NHS Act 2006 restricts free care to those who are "ordinarily resident" here.[3] If treatment is refused, the consequences can be dire. Last year, University College Hospital, Cardiff, refused long term treatment to Ama Sumani, a Ghanaian woman with multiple myeloma. Once her condition had stabilised, she was returned home where limited treatment was available. There was understandable outrage when she died two months later.[4]

But this is not just about single cases. The NHS cannot provide an international service and a balance exists between common humanity and the duty of solidarity to NHS patients. In 2005, the National Audit Office estimated that about 283 000 failed asylum seekers were living in the United Kingdom.[5] No one knows the exact figure, and—if we add "undocumented" immigrants—the total needing NHS care is higher.[6] Some will have chronic illnesses and will need expensive treatment. Yet hospitals are constrained by finite budgets, and treating visitors without charge has opportunity costs. Which NHS patients should we divert care from to do so? This question is inescapable and unsettling.

This dilemma is dealt with by the Overseas Visitors Regulations[7] and non-legal explanatory guidance from the Department of Health.[8] Both were called upon in the case of YA, a 35 year old Palestinian man with liver disease who was previously a member of Hamas. He arrived in England in July 2005 and applied for political asylum. His application was refused in December 2005 on the grounds that he was here for medical reasons, not the fear of persecution at home. He has received NHS treatment but cannot pay for it. However, he cannot return to the Middle East because the Israeli authorities will not permit Palestinians to return to the occupied territories. What right does he have to NHS treatment?

Trusts must assess firstly whether the patient is ordinarily resident in the UK, and if not, whether the patient is eligible for NHS care under the Overseas Visitor Regulations, and if so, whether he or she must pay for it. The regulations contain exceptions permitting access to free NHS care; in particular, those seeking asylum and those who have had "lawful residence" here for at least 12 months before they needed care. Also, subject to reasonable steps being taken to recover payment, doctors have a duty to provide care that involves an emergency, is urgent, or is immediately necessary.

What about failed asylum seekers who are awaiting removal from the UK, however? In March 2009, the Court of Appeal reversed the judgment of J Mitting and held that YA is here "under sufferance." He is not ordinarily resident because "the purpose of the National Health Service Act is to provide a service for the people of England and that does not include those who ought not to be here. Failed asylum seekers ought not to be here." And neither, it said, does YA have lawful residence under the regulations because "one resides here lawfully when one has the right to do so. An indulgence is granted to a claimant for asylum . . . Being here by grace and favour does not create that necessary foundation." Therefore, YA had no "right" to NHS treatment.

In this case, does the NHS have "discretion" to provide care before it is immediately necessary to a

patient like YA who cannot return home, even though he cannot pay? Here the guidance is silent. The Court of Appeal held that there was discretion to treat in these circumstances, but that the guidance was unlawful for failing to advise hospitals how to proceed. On 2 April 2009, the Department of Health responded with interim advice that if a patient's needs become urgent "because . . . they are no longer able or likely to return home within a medically acceptable time, then they should be provided with treatment even if payment cannot be secured in the meantime."[9] But knowing who is "unable or unlikely to return home" and what is a "medically acceptable time" will often be unclear, and because hospitals will not be paid for these patients, there is an incentive not to admit them.

The consequence may be that increased numbers turn to general practitioner surgeries, but the guidance does not extend to primary care.[10] General practitioners must provide immediately necessary care.[11] For non-urgent cases, however, access to free NHS care depends on the general practitioner's willingness to ask difficult and sensitive questions or require documentary evidence of immigration status. This gives general practitioners unwelcome responsibility where they have no legal expertise, and it encourages inconsistency.

Clearly, the matter needs a comprehensive review, and the Department of Health expects to issue new guidance for both primary and secondary care in the autumn. However, as the NHS becomes more transparent, further extension of free care to overseas visitors will test the limits of social solidarity.[12] The integrity of the NHS is built on a system of mutuality and redistributive ethics, "in which citizens accept the benefits of contributing to a common source of welfare." It is humane and decent to provide this care, but we cannot ignore the pressure it imposes on finite NHS budgets.

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Perinatal mortality in the Netherlands

Consistently poor performance indicates that it is time for change

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The Netherlands' consistently poor performance in the European perinatal mortality league is a cause for concern. Neither the concern nor the performance are new. They culminated in the late 1970s and mid-1980s when home births were erroneously put forward as the explanation.[1] A new height was reached when the Peristat project showed that at the turn of this century the Netherlands had the highest perinatal mortality in the European Union.[1] Five years on, nine new EU members have expanded the league from 15 to 24, but this has brought little change.[2] In 2004, perinatal mortality was 10 per 1000 in the Netherlands, higher than in all but one of the new EU members,[2] and still 9.8 per 1000 in 2006.[3]

Admittedly, the European perinatal mortality league is a poor relation of the European football league, not just because it takes four years before the results are announced.[2] Not all teams play by the same rules. Some nations register births for babies ≥500 g; others from 22, 24, or 28 weeks' gestation; and some have different rules for live births and stillbirths.[2] Methods for ascertaining these differ too, and—not infrequently—there are often large discrepancies between the actual number of deaths and the number that are registered.[4 5] So, all teams decide for themselves whether a point was made or not. There is no umpire to ensure equity in rules and ascertainments and no video taped playback to verify this. Although we assume that fair play prevails, national pride in reaching the top should never be underestimated.

Not all perinatal deaths are registered.[4] Registration is influenced by maternity benefits, birth premiums, funeral obligations, and abortion policies, such as whether terminations are legal, until what stage in pregnancy they are allowed, and how they are registered.[2]

So, what is the cause of the Netherlands' poor performance? Over the years explanations have shifted from home birth to better registration; a higher proportion of older mothers, twin pregnancies, and ethnic minorities; lack of screening for congenital anomalies; and non-intervention policies around severely preterm birth. Unfortunately, the media have shed more heat than light on whatever explanation is on offer.

Better registration is an issue. Undoubtedly, the former low mortality (before the 1970s) was based on extensive under-registration,[1 4] not just at the borderline of fetal viability.[1] Is it better now? In contrast to its southern neighbour, Flanders, which has a single register, the Netherlands has three—a national register for primary maternity care (LVR1), another for secondary care (LVR2), and a third for neonatal care (LNR). A great deal of pride and energy is invested in combining these to avoid double counting.[6] A further registry (PRN) has

been devised for that purpose, but it still registers fewer late neonatal deaths than the civil registration.[5]

Participation in the LNR has never been good. In 2000, Dutch data lagged a year behind data from the other EU members. In 2004, births attended by general practitioners (about 5% of the total number) were still missing, and participation was incomplete.[7] Nationwide registration of in vitro fertilisation has been available since 1996, but pregnancy outcomes were lacking until 2003. Registration is certainly better, but is it good enough?

Ethnic origin is also complex. It is illegal to register ethnicity in several EU countries,[8] and data are available only for nationality or country of birth.[2] In the Netherlands, ethnic origin is defined as being of Dutch ancestry or not of Dutch ancestry (this last group is often differentiated into Western or non-Western, although the distinction is somewhat unclear).[8] The criteria of the Netherlands' bureau for statistics do not match those of the perinatal registrations, and classification depends on the perception of the health professional who registers the birth.[9] Much attention has been devoted to the health outcomes of people of non-Western origin. As a group, their outcomes are poorer than for people of Dutch origin, but the factors that contribute to this—such as poor use of health services and the high incidence of congenital malformations, preterm birth, teenage pregnancy, grand multiparity, and single mothers—vary among different ethnic groups.[9]

People of non-Western origin are mainly concentrated in the large cities. In 2002-6, 43% of births in the four largest cities (Amsterdam, Rotterdam, the Hague, and Utrecht), were among these ethnic groups compared with 11% in the rest of the country.[10] Perinatal mortality is higher in these cities than in the rest of the country (11.1 per 1000 *v* 9.3 per 1000), even though there are fewer congenital malformations (22 per 1000 *v* 25 per 1000), probably because of better access to screening and termination of pregnancy.[10] However, in the underprivileged suburbs, non-Western people invariably have lower perinatal mortality than people of Western origin.[10] Also, mortality in the rest of the Netherlands is higher in people of Western (8.8 per 1000) and non-Western (12.8 per 1000) origin than in 19 EU countries that register deaths from 500 g or 22 weeks onwards.[2 10]

Dutch maternity care has a long tradition of not being proactive,[7 11] in the confidence that Mother Nature knows best. This has also resulted in high maternal mortality from hypertensive disease, mostly because diagnosis and treatment came too late.[12]

There are indications that things are changing.[7] Denial of the poor performance has dissipated, ultrasound screening has been instituted, and audits of various kinds have sprung up.[7] Whether these changes will improve outcomes remains to be seen.

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The FDA and the Declaration of Helsinki

A new rule seems to be more about imperialism than harmonisation

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The Food and Drug Administration (FDA) of the United States has ruled that clinical trials performed outside the US no longer have to conform to the Declaration of Helsinki if used to support applications for registration of products in the US.[1] Instead, the International Conference on Harmonisation Good Clinical Practice (GCP) has been designated as the new regulatory standard. This suggestion met considerable opposition from scientists, ethicists, and consumer groups before and during the consultations.[1-3] The FDA's justifications included the arguments that it was merely harmonising its regulations with a global standard, and that legal instruments, such as the US Code of Federal Regulations, cannot embed external documents subject to change beyond the agency's control (dynamic referencing).[1 4]

This justification failed to explain why GCP was any different in this respect, or why the declaration and the GCP were considered mutually exclusive.[2] Although such dynamic referencing can create legal problems,[5 6] because legislatures cannot unreservedly commit to indefinite amendments, the declaration can, and should, be considered a minimum standard that reflects core ethical principles, operationalised through instruments such as the GCP and national regulatory policy. Static referencing of specific versions has not created substantial problems to date, and no reason is given about why this should be a problem now. The concerns remain unresolved,[7] but the question of what impact the change will make needs to be answered at both the instrumental (direct) level and the symbolic (indirect) level.

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At first sight, the potential impact seems relatively small. Only a subset of clinical trials performed outside the US are affected, and supporters (mainly from industry) see the differences between the two documents as relatively minor. The real impact cannot be accurately ascertained at present, but it may be much greater than claimed because the US is the world's largest drug and medical device market.[7] In addition, increasing globalisation and movement of clinical trials "off shore" mean that a large proportion of such trials will be used in applications for marketing in the US.[8 9]

Some of the differences between the documents, such as those relating to the use of placebo controls in trials, are important and may have motivated the FDA to make this change. The fourth revision of the Declaration of Helsinki (1996) created difficulties for the FDA by restricting the use of placebos where proved interventions had become established. This had major implications for research in resource poor nations, where placebos were being used in such situations.[5] Despite heated debate,[10] the World Medical Association (WMA) has stood firm on the principle of not withholding effective interventions in its most recent (sixth) revision of 2008.[11] The FDA's decision therefore seems to reinforce its defence of placebo controlled trials.

Whatever the instrumental impact, in light of this history it is the symbolic aspects of the decision that should concern us most.[2 8] The withdrawal of an unproblematic reference has far more significance than simply omitting it. We have grave misgivings about the future of international ethical norms, at least in the US. Despite assurances by the FDA, GCP is not an ethical code, but a procedural regulatory manual based on the regulatory frameworks of the US, Japan, and Europe. Thus, it is a description of existing procedures, not an aspirational document.

It is not the procedural nuances that are at stake, but rather the moral reasoning that forms the basis of a culture of ethically responsible research.[5 11 12] The declaration, along with other international ethical guides,[5] remains a signpost for the collaborative development of international ethical principles and practice, the influence of which far exceeds national laws and regulations, and which was extended further in the 2008 revision. The declaration is the primary source and arbiter of research ethics worldwide. It guides legislation and the ethical conduct and oversight of research, particularly in developing countries, which are the site of an increasing share of clinical research.

This symbolic move away from the declaration contrasts with its growing recognition elsewhere. Although not explicitly part of international or national law, the legal status of codes of ethical principles is recognised. The US Court of Appeals ruled that the declaration (and other conventions) constituted a sufficient customary norm to be considered binding in the Pfizer trovafloxacin case in January 2009.[13] The court reversed a dismissal by a lower court of a lawsuit by families of children who had died or were injured in a Nigerian meningitis trial. The children had received this experimental antibiotic, and the court ruled that the declaration established a universal norm prohibiting non-consensual experimentation. At a time of growing concern about the politics and increased globalisation of biomedical research, a more international view of research ethics is needed, rather than primacy of national policies that fall short of accepted principles.[9]

The FDA is at best acting as if its standards are distinct from globally accepted norms by pressuring the declaration to agree to its demands. At worst, it is creating an impression that it is more interested in facilitating research than respecting the rights of people who are the subjects of research. This has been variously depicted as entrenching different standards for different parts of the world (ethical pluralism),[5 8] establishing the US's right to unique policies (exceptionalism),[2] and one country imposing standards on others (moral imperialism).[8] We must hope that the new administration in Washington will review the FDA's ill advised actions.[7]

The declaration and the WMA's International Code of Ethics contain the crucial statement that a doctor or investigator's conscience and ethical duty of care must transcend national laws. To be compliant with national laws that respect basic human rights and ethical norms is necessary, but is not in itself a sufficient standard.

How then can we best protect ethical principles in research? Historically, individual conscience, training, and ethical culture were considered sufficient. These have repeatedly fallen short of expectations, however, given the political, social, and fiscal contexts in which research occurs, with its potential for power differentials and conflict of interest. If organisations such as the FDA are unable or unwilling to foster an international culture of ethical research, it must fall to others, such as professional associations, to ensure that ethical reasoning is as central to research as it is to care,[10] and that ethical oversight has sufficient powers and resources to be effective. Although transgressions of ethical codes sometimes invite administrative and criminal sanctions, all professional associations have a responsibility to scrutinise the ethical competence, capacity, and practice of their members' research. Ultimately, ethically responsible research remains a collective responsibility.[5]

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